UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,506	02/26/2004	Darwin J. Prockop	57616-5001-03	4991

23973 . 7590 05/31/2006

DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA, PA 19103-6996

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/787,506	PROCKOP ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the preliminary amendment filed February 26, 2004, canceling claims 1-54, and adding new claims 55-77. Claims 55-77 are pending in the application and under current examination.

Priority

The instant application is a continuation of the prior filed application 10/423,232, filed 4/25/2003, that is a continuation of application 08/913,918 filed 12/8/1997 and PCT/US96/04407 filed 3/28/1996, that is a continuation in part of 08/412,066, filed 3/28/1995. Support for the claims of the instant application cannot be found in the parent application, 08/412,066. Specifically, 08/412,066 specification discloses methods of generating bone cartilage or lung defects and treating patients suffering from disease, disorder or condition characterized by bone cartilage or lung defects comprising administration of bone marrow stromal cells. However, the specification lacks disclosure that the method can be used to generate, repair, or regenerate blood vessels in a mammal. The 08/412,066 specification further does not contemplate methods of treating defects in the blood vessel of a mammal. Therefore, the effective filing date of instant claims is 3/28/1996.

Claim Objections

Applicant is advised that should claim 56 be found allowable, claim 70 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112 - Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for methods of generating, or repairing a blood vessel in a mammal, in a tissue specific manner or treating any disease, comprising administering to said mammal, autologous, or allogeneic or syngeneic bone marrow stromal cells, or for the treatment of a vascular disorder.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

The claims encompass methods for generating, or repairing blood vessels in a mammal by administering systemically or intraperitoneally, autologous, allogeneic or syngeneic bone marrow stromal cells wherein the cells differentiate into various cell

types, thus forming blood vessels. The claims further embrace a method for treating a disease, disorder, or condition in a mammal characterized by a defect in a blood vessel, such that the vessel is regenerated or repaired. The nature of the invention is extremely broad, given that a general systemic administration of stromal cells would specifically target a broad and diverse genus of conditions characterized by a defect in a blood vessel. Such methods therefore require an enabling disclosure.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the person of skill in the art (Artisan) would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to demonstrate that systemic or intraperitoneal administration of stromal cells would result in the proper differentiation and generation or repair of blood vessels at the site where said blood vessels are required, and not at undesired sites, for the methods of the instant application.

The Amount Of Direction Or Guidance Presented And Working Examples

The instant specification teaches that the invention is "based upon the discovery that stromal cells introduced into patients by the bloodstream, develop into bone cartilage and lung". Applicants additionally state: "Similarly, it is believed that stromal cells will also develop into cells of the dermis, blood vessels, heart and kidneys, or throw off daughter cells that will do so." (page 8, line 14-29). The methods of the instant disclosure are specifically directed toward introduction of stromal cells into transgenic mice by intravenous injection for the purpose of development of bone and other connective tissues (Example 1, p. 31). As general guidance, applicants teach that administration of cells involves plating of stromal cells onto plastic, removal of the adherent cells from the culture dishes, and injection in the tail vein of each mouse (lines 11-17, p. 32). The specification notes that donor cells from marrow are partially enriched for mesenchymal precursors (lines 24-25, p. 31), and that most of the cells were fibroblast-like, but a few macrophages and adipocytes were also seen (lines 8-10, p 32).

Specifically, the application demonstrated that implantation of recombinant donor cells from marrow partially enriched for mesenchymal precursors from normal mice expressing collagen I into irradiated transgenic mice led to production of progeny cells that express the transgene (pp. 33-36). These cells were said to efficiently populate several connective tissues and diffusely incorporated into the mesenchymal parenchyma of the lung (lines 15-17, p. 34). A prophetic scenario for comparing the infusion of MSCs intravenously versus intraperitoneally is indicated in Example 4. However, no means or methods for the systemic or intraperitoneal administration of MSCs for the generation or repair of blood vessels, for any disease, disorder or conditions are provided.

The specification fails to show the generation, or repair of blood vessels in the mice following intravenous administration of MSCs in mice.

The specification is silent on the demonstration of how systemic administration of MSCs by intravenous injection, or intraperitoneal administration would lead to angiogenesis or vascularization at a desired site, instead of or in addition to connective tissues and the mesenchymal parenchyma of the lung. This is further complicated by the fact that the cells cultured and administered to the mice are a mixed population and not a

purified population of MSCs. Therefore, it would require further experimentation to demonstrate the ability to achieve neovascularization or repair of blood vessels in numerous disease conditions, as instantly claimed.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses bone marrow stromal cells that are cultured from mice and the subsequent intravenous administration of the adherent cells obtained therefrom, to mice, resulting in the population of connective tissues and mesenchymal parenchyma of the lung.

The State Of The Prior Art And The Unpredictability Of The Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art with regard to the transplantation of bone marrow stromal cells (MSCs) is effectively summarized by the references of Caplan et al. (U.S. Patent No. 5,197,985; filed Mar. 30, 1993), and Wilson et al. (U.S. Patent No. 5,817,773; filed Feb. 23, 1996). Caplan et al. teach the implantation and differentiation of marrow-derived mesenchymal stem cells for treatment of skeletal and other connective tissue disorders (Abstract). Caplan et al. teach applying the culturally expanded purified marrow-derived mesenchymal cells to a desired area of connective tissue that is damaged, by means of a vehicle of carrier, that is a porous ceramic composition (columns 1 and 2). Wilson et al. teach the differentiation or culture of stem cells derived from stromal cells and mesenchymal stem cells and their engrafting *in vivo* (lines 25-39,

column 6). The authors describe the culture of bone marrow stromal cells and discovered that bFGF delayed senescence and increased their proliferative potential (Example 1, columns 21-22). The art at the time of filing of the instant application is silent however, on the use of MSCs for differentiation into blood vessels and neovascularization.

Insight into the application of MSCs for the generation of blood vessels and angiogenesis may be obtained from the post-filing art of Nagaya et al. (Am. J. Physiol. Heart Circ. Physiol. 287:H2670-H2676; 2004), Zisch, et al. (Curr. Opin. Biotech. 15:424-429; 2004), and Dzau et al. (Hypertension 46:7-18; 2005). Nagaya et al. state that MSCs are pluripotent cells that differentiated into a variety of cells, including cardiomyocytes and endothelial cells, and show that the intravenous administration of MSCs in rats can lead to angiogenesis and myogenesis (Abstract). Nagaya et al. further state that MSCs may contribute to neovascularization not only through their ability to generate capillary-like structures in the myocardium, but also through growth factor-mediated regulation (second column, p. 2675). Further, they noted a low percentage of MSC migration to the heart, and further showed only a small percentage of transplanted MSCs were incorporated into the heart (first column, p. H2676). These observations are important considerations in the use of MSCs in any treatment method, as they highlight the difficulty of delivery of MSCs to a particular target site, and the potential for detrimental neovascularization at physiological locations where such vascularization is not required. Moreover, Nagaya et al. note : "A limitation of this study is that the cell population may be mixed, rather than limited to MSCs" (first column, p. H2676). The cultured stromal cells of the instant invention are similarly a mixed population of cells.

Zisch et al. describe the application of autologous endothelial stem/progenitor cells (EPCs) derived from bone marrow, for incorporation into sites of new vessel growth for the improvement of regional blood flow (Abstract). The authors note that improvements in perfusion of recipient tissue is unlikely to result from the cell replacement alone, but instead stems from the provision by EPCs of paracrine growth factor/cytokine signals. Additionally stating: "The interaction between the host environment and EPCs has not been well established...the surprising plasticity of primary EPCs to change fate into cardiomyocyte or mesenchymal phenotypes warrants

further investigation" (second column, p. 427). These observations indicate that the plasticity of the stem cells can result in the cells developing into a number of different cell types, which is important in light of the systemic and intraperitoneal routes of administration of the instant claims, wherein administered MSCs could be transplanted at numerous sites in a mammal, causing potential undesired differentiation. Further, following said implantation, the MSCs, would likely alter the physiological state of the mammal by providing paracrine growth factor/cytokine signals.

The foregoing is expanded upon by Dzau et al., stating: "EPCs from patients with cardiovascular diseases display varying degrees of functional impairment. Aging and diabetes markedly reduce the availability and impair the function of EPCs. Because older and diabetic patients are the most vulnerable populations for cardiovascular diseases, this severely restricts the ability to treat with autologous EPCs the patients who theoretically need them most. The purity and developmental stage of the cells used for transplantation are important factors. Yoon et al. reported recently that injection of total bone marrow cells into the heart of infracted rats could potentially lead to severe intramyocardial calcifications. Thus, this finding brings attention to the potential risks of transplanting unselected bone marrow cells and cautions against their premature use in the clinical setting. Exogenous mobilization of bone marrow with hematopoietic growth factors and other endothelial growth factors may recruit progenitor cells to sites of occult neoplasia, leading to vascularization of dormant tumors. In addition, mobilization could potentially accelerate progression of atherosclerotic plaque by recruiting inflammatory and vascular smooth muscle cell progenitor cells into the plaque, contributing to neointima hyperplasia and transplant arteriopathy...Finally, there has been one study that has shown evidence that EPC may themselves contribute to allograft vasculopathy by promoting neovascularization of the plaque." (first column, p. 15).

Hence, the nature of the invention is not reasonably predictable given the lack of guidance in the specification, for the generation, repair or treatment of conditions requiring vascularization, following systemic or intraperitoneal administration of MSCs, and would require further and undue experimentation. Because of the immaturity of the art, its complexity, and its unpredictability, as shown by the other factors, one of skill in

the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The claims of the instant application are drawn to methods of generating, repairing and treating conditions that involve neovascularization and angiogenesis, not apparent from the disclosure of the invention. Therefore, in light of the guidance provided by the disclosure of the application and the unpredictability of the art, it would require undue experimentation by the skilled Artisan to carry out the experiments required to demonstrate that applicant is enabled for methods of systemically or intraperitoneally administering bone marrow stromal cells, to generate a blood vessel in a mammal. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Quantity Of Experimentation

The invention recites a broad and diverse genus of vascular disease, conditions and disorders that are to be treated by administration of MSCs. The quantity of experimentation in the area of stem cell differentiation and transplantation is extremely large, as there are a significant number of parameters, which would have to be studied and tested, given the broad scope and complex clinical nature of the conditions, to definitively show that one is enabled for the methods of systemically or intraperitoneally administering bone marrow stromal cells, to generate a blood vessel and treat vascular disease in a mammal. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. The lack of guidance in the specification, the unpredictability of the art, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Analysis And Summary

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed

invention. The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. In the instant case, and for the specific reasons cited above, in a highly unpredictable art where the mechanisms underlying MSC cell differentiation remain to be elucidated, together with the large quantity of research required to define these unpredictable variables, including the targeted delivery of MSCs to a desired site and the prevention of inappropriate neovascularization or unwanted angiogenesis, that may be applied to the treatment of numerous vascular diseases by systemic administration of stromal cells, and the lack of guidance provided in the specification regarding the same, it is the position of the examiner that it would require undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 55-56, 59-60, 63, 66-67, 70-71, and 74-75 are rejected under 35 U.S.C. 102(a) as being anticipated by Boisvert et al. (J. Clin. Invest. 96:1118-1124, 1995).

When given the broadest reasonable interpretation, the claims encompass a method comprising administering autologous or allogeneic bone marrow stromal cells (with or without enrichment for mesenchymal stromal cells) to a mammal, wherein said cells differentiate into cells of a blood vessel in said mammal.

Boisvert et al. teach a treatment for severe hypercholesterolemia in mice by transplantation of bone marrow from normal wild-type mice (Title and Abstract). The mice subjected to transplantation treatment suffered from atherosclerotic lesions of the blood vessels (Figure 7, p. 1123; limitation of claim 56). Therefore, the limitation of peripheral vascular disease (claim 71) is also encompassed by the hypercholesterolemic mice. Bone marrow stromal cells were obtained from allogeneic wild type mice and administered systemically via injection in the tail vein (first column, p. 1119; limitation of claims 59-60, 66-67 and 74-75). While Boisvert et al. do not teach the differentiation of administered stromal cells into cells of a blood vessel, the ability of MSCs to differentiate into cells that include those of blood vessels is an inherent property of these cells, that is relied upon by the instant invention. Therefore, the isolated bone marrow stromal cells of Boisvert et al. must necessarily possess the ability to differentiate into cells of a blood vessel following administration to a mammal.

Therefore, each and every element and limitation regarding the methods of claims 55-56, 59-60, 63, 66-67, 70-71, and 74-75 is anticipated and effectively addressed by Boisvert et al., absent evidence to the contrary.

Claims 55, 58, 62-63, 65, 69-70, 73, and 77 are rejected under 35 U.S.C. 102(e) as being anticipated by Caplan et al. (U.S. Patent No. 5,197,985; filed Nov. 16, 1990).

Caplan et al. describe methods for enhancing the implantation and differentiation of marrow-derived mesenchymal cells (Abstract). Caplan specifically teaches the isolation, purification, culture and expansion of marrow-derived mesenchymal cells derived from human patients (columns 9 and Table 1; limitations of claims 58, 65 and 73). Caplan further teaches the loading of the cells in diffusion chambers and surgically implanting them intraperitoneally into nude mice (column 13, limitation of claims 62, 69 and 77). The transplantation method of Caplan et al. is directed to the treatment of skeletal or other connective tissue disorders in humans (Abstract, limitation of claims 64, 70 and, 72). While Caplan et al. do not teach the differentiation of administered stromal cells into cells of a blood vessel, they describe applying the isolated, purified and culturally expanded stem cells to a porous carrier and implanting the cells into an

environment containing factors necessary for differentiating the human mesenchymal stem cells into bone cells (claim 1). The formation of bone in a living mammal additionally requires vascularization. The ability of MSCs to differentiate into cells that include those of blood vessels is an inherent property of these cells, that is relied upon by the instant invention. Therefore, the isolated bone marrow stromal cells of Caplan et al. must necessarily possess the ability to differentiate into cells of a blood vessel following administration to a mammal.

Therefore, each and every element and limitation regarding the methods of claims 55, 58, 62-65, 69-70, 72-73, and 77 is anticipated and effectively addressed by Caplan et al., absent evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 57-58, 61, 64-65, 68, 72-73 and 76 are rejected under 35 U.S.C. §103(a) as being unpatentable over Boisvert et al. (J. Clin. Invest. 96:1118-1124, 1995), in view of Enright et al. (Curr. Opin. Hematol. 2(4): 293-299; 1995).

Boisvert et al. teach a treatment for severe hypercholesterolemia in mice by systemic delivery and transplantation of allogeneic bone marrow from normal wild-type mice (Title and Abstract). It is also well known in the art that systemic administration may be carried out either intravenously or intra-arterially (limitation of claims 61, 68, and 76). The mice subjected to transplantation treatment suffered from atherosclerotic lesions

of the blood vessels (Figure 7, p. 1123). Boisvert et al. do not describe the use of humans as donors or recipients of bone marrow stromal cells. However, Boisvert et al. state that "the data suggest that a bone marrow transplantation may permanently treat hypercholesterolemia that leads to arthrosclerosis and cardiovascular disease." (first column, p. 1123). Therefore, Boisvert et al. provide the motivation to extend bone marrow transplantation for the treatment of blood vessel disorders to other animals that include humans.

Enright et al. describe the treatment of human patients with chronic myelogenous leukemia, by matched sibling donor marrow transplantation as well as autologous marrow transplantation (Abstract). Thereby showing that the mouse model of Boisvert et al. may be applied to human bone marrow transplantation with a reasonable expectation of success.

Given the teachings of Boisvert et al. as stated *supra*, regarding the systemic administration of allogeneic bone marrow stromal cells for treatment of conditions affecting blood vessels, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the transplantation method of Boisvert et al., in combination with the human whole bone marrow transplantation method of Enright et al. to generate a blood vessel in a human (claims 57, 64, and 72).

Therefore, a person of ordinary skill in the art, would have been motivated to combine the atherosclerosis treatment using allogeneic stromal cells, described by Boisvert et al., and the human bone marrow stromal cell transplantations described by Enright et al., thus resulting in the blood vessel generating methods of the instantly claimed invention with a reasonable expectation of success, because the combination of the systemic administration method of Boisvert et al. and the human marrow cell transplantation methods of Enright et al., would result in the generation, repair or treatment of blood vessels in a human subject.

Claims 62, 69, and 77 are rejected under 35 U.S.C. §103(a) as being unpatentable over Boisvert et al. (J. Clin. Invest. 96:1118-1124, 1995), in view of Enright et al. (Curr. Opin. Hematol. 2(4): 293-299; 1995), a applied to claims 57-58, 61, 64-65, 68, 72-73 and

76 above, and further in view of Caplan et al. (U.S. Patent No. 5,197,985; filed Nov. 16, 1990).

Boisvert et al. describe systemic delivery and transplantation of allogeneic bone marrow from normal wild-type mice (*supra*). Enright et al. describe matched sibling donor marrow transplantation as well as autologous marrow transplantation in humans (*supra*). Neither Boisvert, nor Enright describe the intraperitoneally administered transplantation of bone marrow stromal cells, but envision systemic delivery for treatements that involve the differentiation of marrow stromal cells at the appropriate and required sites of treatment, thus providing the motivation to administer stromal cells at any site in the body.

Caplan et al. describe methods for enhancing the implantation and differentiation of marrow-derived mesenchymal cells (Abstract). Caplan specifically teaches the isolation, purification, culture and expansion of marrow-derived mesenchymal cells derived from human patients (columns 9 and Table 1; limitation of claims 58 and 73). Caplan further teaches the loading of the cells in diffusion chambers and surgically implanting them intraperitoneally into nude mice (column 13, limitation of claims 62, 69, and 77). The transplantation method of Caplan et al. is directed to the treatment of skeletal or other connective tissue disorders in humans (Abstract).

Therefore, a person of ordinary skill in the art, would have been motivated to combine the atherosclerosis treatment using allogeneic stromal cells, described by Boisvert et al., and the human bone marrow stromal cell transplantations described by Enright et al., and the intraperitoneal transplantation method of Caplan et al. thus resulting in the blood vessel generating methods of the instantly claimed invention with a reasonable expectation of success, because the combination of the systemic administration method of Boisvert et al. and the human marrow cell transplantation methods of Enright et al., when administered intraperitoneally would result in the generation of blood vessels in a human subject.

Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the transplantation method s of Boisvert et al., and Caplan et al., in combination with the human whole bone marrow transplantation

method of Enright et al. to intraperitoneally administer marrow cells, and to generate a blood vessel in a human

Hence, the claimed invention a whole is *prima facie* obvious, absent evidence to the contrary.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 55-77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55-70 of copending Application No. 10/423,232. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims recite a process comprising administering autologous or allogeneic bone marrow stromal cells to a mammal. The claims of the '232 application are directed to processes for generating, regenerating or repairing heart tissue wherein the bone marrow stromal cells differentiate into heart cells, that encompass the methods for generating, regenerating or repairing blood vessels wherein the bone marrow stromal cells differentiate into blood vessels (claims 55-77 of the instant application). Claims reading on heart tissue encompass the vasculature of the heart tissue, hence, the claims of copending Application No. 10/423,232 anticipate and fall entirely within the scope of the rejected claims of the instant application.

Claims 55-77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-28 of copending Application No. 10/844,235. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Both sets of claims recite a process comprising administering allogeneic bone marrow stromal cells to a mammal. The claims of the '235 application are directed to processes for generating, ablated marrow and enhancing hematopoiesis and hematopoietic recovery, that encompass the methods for generating, regenerating or repairing blood vessels.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

Q. JANICE LI, M.D.
PRIMARY EXAMINER